

A close-up photograph of a young girl with dark hair in pigtails, secured with blue hair ties. She has her eyes closed and is gently holding her cheeks with both hands. She is wearing a yellow garment. The background is a soft-focus garden scene with large green leaves and bright red tulips.

Pharmaceutical
Aerosol

Content

- Components, Formulation
- Different system of aerosol
- Manufacturing, Large scale production equipment
- Evaluation of aerosol
- Operation of an aerosol package- oral, inhalation, nasal and topical aerosols.

Definition

Aerosols: Aerosols are a system of finely divided liquid or solid particles dispersed in and surrounded by a gas.

An aerosol (Pressurized package) is defined as a system that depend on the power of a **compressed or liquefied gas** to expel the **contents** from **the container** with **special valve system**.



Examples



Uses of pharmaceutical aerosols

When kids with cancer were asked about the toughest part of having cancer, many of them said it's the needle stick.

“How wonderful that researchers are working on ways to eliminate many of the needles that children faces”.

<http://www.drgreene.com/aerosol-form-measles-vaccine/>

It's not funny when you're next! 😂



Uses of pharmaceutical aerosols

- **Topical**

- Local anesthetics
 - (e.g. Benzocaine)
- Wound washing
- Rubiferants
 - (e.g. Methylsalicylate)
- Spray on bandages
- Proprietary burn applications
- Antibacterials
 - (e.g. Neomycin)
- Antifungal sprays
 - (Miconazole)
- Anti-inflammatory steroids
 - (e.g. Dexamethasone)

- **Oral and Lingual**

- Local anesthetics
 - (e.g. Lidocaine)
- Antiseptics
 - (e.g. Chloroseptic)
- Anti-anginals
 - (e.g. Nitroglycerin)

- **Rectal**

- Local anesthetics
 - (e.g. Pramoxine)
- Anti-inflammatory steroids
 - (e.g. Hydrocortisone)

Uses of pharmaceutical aerosols

- Nasal
 - Decongestants (e.g. Phenylephrine)
 - Anti-inflammatory steroids (e.g. Beclomethasone)
 - Anti-allergics (e.g. Cromolyn sodium)
 - Moisturizers (e.g. Normal saline)
 - Systemic access
 - Antidiuretics (e.g. Desmopressin)
 - Antismoking (Nicotine)
- Ocular
 - Contact lens cleaning solutions
 - (not applied directly to eye)
- Respiratory
 - Bronchodilators (e.g. Albuterol)
 - Anti-inflammatory steroids (e.g. Beclomethasone)
 - Antiallergics (e.g. Cromolyn sodium)
 - Antivirals (e.g. Ribavirin)
 - Smoking cessation (e.g. Nicotine)
 - Migraine (e.g. Ergotamine tartrate)

Advantage

- Portable
- Easy to use and convenient
- Minimal contamination to unused products
- Maintains sterility
- Enhances stability (prevents from external environment like light, Moisture, O₂)
- Delivered directly to the affected area, even to hard to reach site (nasal, oral), in a desired form (spray, stream, quick breaking foam, stable foam)
- Provide access to systemic circulation
- Expands to fill available space and provide complete surface area coverage.
- No need to touch target site
- No irritation (esp. in topical preparation)
- Ease and convenience of application
- Application of medication in a thin layer

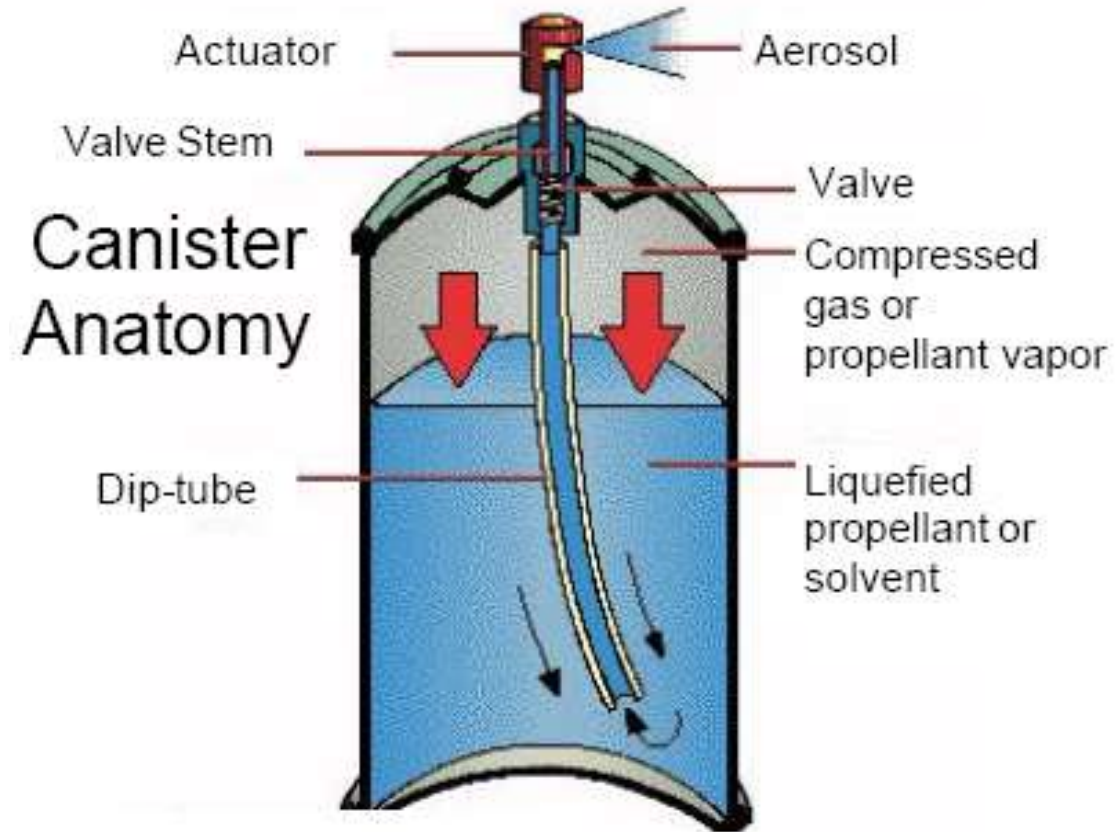
Disadvantages

- Expensive
- Performance can deteriorate during life of product
- Limited safety hazard
 - Flammable
 - Pressurized
 - Unintended inhalation
- Sometimes prone to incorrect use

Components of Aerosol Package

An aerosol Package consists of

- **Propellants** (The fluorinated hydrocarbons find widespread use in most aerosols. Other propellants includes hydrocarbons including propane, butane, and isobutane, and compressed gases such as nitrogen, carbon dioxide, and nitrous oxide (N₂O).)
- **Container** (tinplate, aluminum, stainless steel, glass)
- **Valve and actuator**
- **Therapeutic agent and Pharmaceutical Excipients** (including diluents, antioxidants and suspending agents)



Propellants

- Propellants are known as heart of the pressurized packs

Functions:

- Generation of pressure so that medicaments can be expelled when valve is opened.
- Function as solvent/dispersing agent depending upon the type of active materials.
- It also affects the characteristics of expelled products like spray, film or foam.
 - Spray: for long time remains in air
 - Film: Produces film on surface treated; aka coarse spray (50 to 200 μm)
 - Foams: Emulsion in propellant forming bubbles

Types of Propellants

Liquefied gases

- Halogenated Hydrocarbon
 - Chlorofluorohydrocarbon
Trichloromonofluoromethane (propellant 11)
Dichlorofluoromethane (propellant 12)
Dichlorotetrafluoroethane (propellant 114)
 - Hydrofluoroalkanes (aka Hydrofluorocarbons)
1,1,1,2,3,3,3 – Heptafluoropropane (HFA-227)
1,1,1,2 – Tetrafluoroethane (HFA-134a)
Difluoroethane (HFA-152a)
- Hydrocarbons
 - Propane (A-108)
 - Butane (A-17)
 - Iso-butane (A-31)

Compressed gases

- Nitrous oxide
- Carbon dioxide
- Nitrogen

Chlorofluorohydrocarbon

- **Advantages**
 - Low inhalation toxicity
 - High purity & chemical stability
 - CFC-11 is a good solvent
- **Disadvantages**
 - Destructive to atmospheric Ozone
 - Contribute to “greenhouse effect”
 - High cost
- Used only in inhalation aerosols
- Gradual replacement of CFCs based MDIs with hydrofluoroalkane (HFA) propellants is widely anticipated.

Hydrofluoroalkanes

- **Advantages**
 - Low inhalation toxicity
 - High purity & chemical stability
 - Not ozone depleting
- **Disadvantages**
 - Poor solvents
 - Minor “greenhouse effect”
 - High cost

Hydrocarbons

- **Advantages**
 - Inexpensive
 - Minimal ozone depletion
 - Negligible “greenhouse effect”
 - Excellent solvents
- **Disadvantages**
 - Flammable
 - Aftertaste
 - Unknown toxicity following inhalation
 - Low liquid density

Compressed Gas

- **Advantages**
 - Low inhalation toxicity
 - High purity & chemical stability
 - Inexpensive
 - No environmental problems
- **Disadvantages**
 - Require use of a nonvolatile co-solvent
 - Produce coarse droplet sprays
 - Pressure falls during use
- Use of compressed gas is typically restricted to its applications where spray characteristics are not critical

Physical properties of propellants

CFC - Physical Properties

Property	CFC-11	CFC-12	CFC-114
Formula	$\text{C Cl}_3\text{F}$	$\text{C Cl}_2\text{F}_2$	$\text{C}_2\text{Cl}_2\text{F}_4$
Flammability limits in air (%v/v)	None	None	None
Boiling point (°C)	23.8	-29.8	-3.8
Vapor pressure at 25°C (Pounds / square inch)	15.3	94.5	31.0
Liquid density at 25°C (g/ml)	1.48	1.31	1.46

HFA - Physical Properties

Property	HFA-134a	HFA-227
Formula	$\text{CF}_3\text{-CFH}_2$	$\text{CF}_3\text{-CFH-CF}_3$
Flammability limits in air (%v/v)	None	None
Boiling point (°C)	-26.1	-16.5
Vapor pressure (bar at 20°)	5.72	3.90
Liquid density at 20°C (g/ml)	1.23	1.42

HC - Physical Properties

Property	n-Butane	Isobutane	Propane
Formula	$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	$\text{CH}(\text{CH}_3)_3$	$\text{CH}_3(\text{CH}_2)\text{CH}_3$
Flammability limits in air (%v/v)	1.9 - 8.8	1.8 - 8.4	2.2 - 9.5
Boiling point (°C)	-0.5	-11.7	-42.1
Vapor pressure at 25°C (Pounds / square inch)	31	45	125
Liquid density at 25°C (g/ml)	0.58	0.56	0.51

Compressed Gas - Physical Properties

Property	Carbon Dioxide	Nitrogen	Dinitrogen Oxide
Formula	CO_2	N_2	N_2O
Flammability limits in air (%v/v)	None	None	None
Boiling point (°C)	-78.3	-195.6	Unknown
Vapor pressure	Depends on fill	Depends on fill	Depends on fill
Liquid density	Not a liquid	Not a liquid	Not a liquid

Mixtures of Propellants

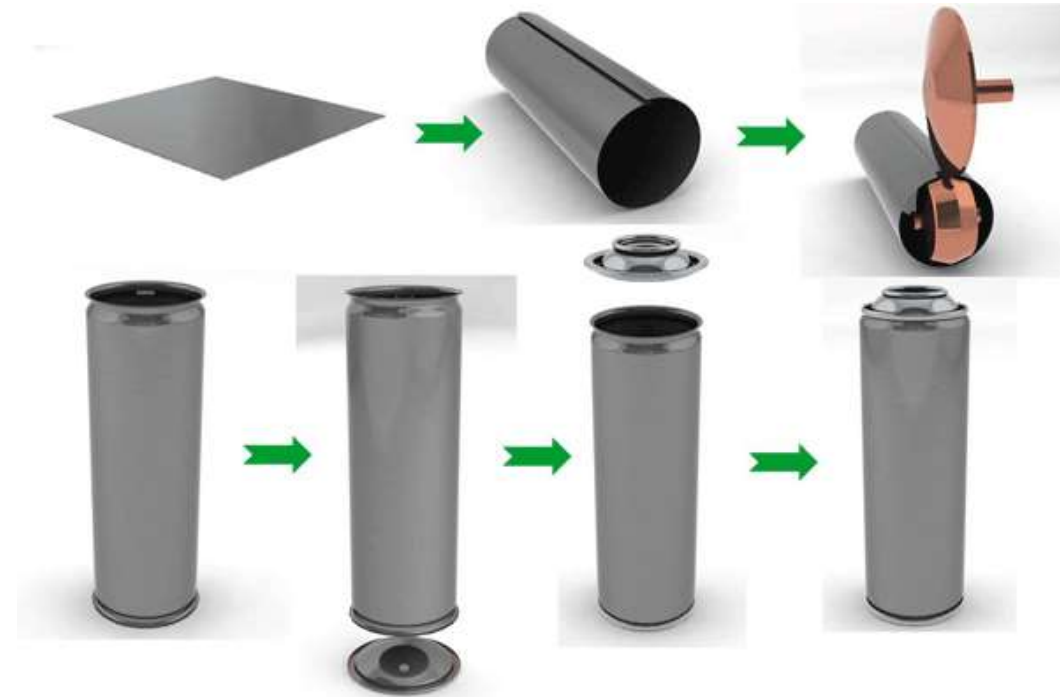
- Allow Variation in
 - Vapor Pressure
 - Fine Particle Fraction / Droplet Size
 - Leakage
 - Choice of Filling Process
 - Liquid Density
 - Irreproducible unit doses
 - Dose to Dose
 - Can to Can
 - Solvency
 - Insoluble or completely soluble OK
 - Partially soluble is a problem

Containers

- Various types of materials can be used
 - Tin plated steel
 - Aluminum
 - Stainless steel
 - Glass
 - Uncoated glass
 - Plastic coated glass
 - Plastics

Containers

- Tin plated container
 - Most commonly used
 - The tin plated steel container consist of a sheet of steel plate that has been electroplated on both side with tin.
 - Not suitable for all products
 - Incompatible with some propellants and solvents
 - Visible seams make them less cosmetic appealing
 - Can be pressurized from the base with compressed gases



Container

- Aluminum Container
 - Lightweight and seamless
 - Visually appealing
 - Easy to fill and crimp
 - Can be anodized or epoxy coated
 - Opaque
 - Used for inhalation and topical aerosols
 - Can be screen printed
 - Incompatible with some propellants and solvents (combination of ethanol and propellant 11 produces hydrogen acetyl chloride, aluminum chloride, propellant 21 and other corrosive products)



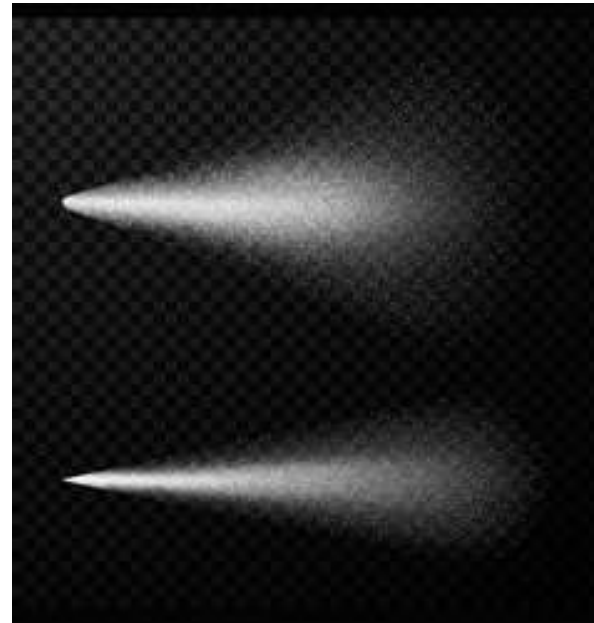
Containers

- Stainless steel
 - Extremely strong and resistance to most materials
 - No internal organic coating is required
- Glass container
 - Transparent
 - Allows level of contents to be seen
 - Coated with plastic to prevent fragments of glass into products during transportation
 - Corrosion problem are not there
 - Allows greater degree of freedom in design of container.
 - Difficult to label / heavy



Valve

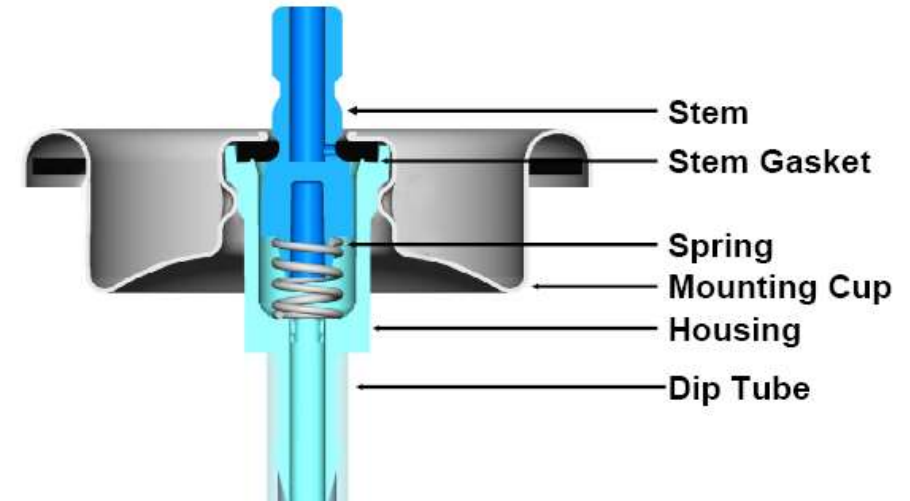
- The primary purpose of valve is to regulate the flow of products from the container.
- It should be capable of
 - Being easily opened and closed
 - Delivering the content in desired form
 - Foam
 - Spray
 - Stream
 - Discharge the desired amount when needed and prevent loss at other time
- Valve used for pharmaceutical usually do not differ from the valve used for non-pharmaceutical aerosol products but
 - Must be approved by FDA
 - May or may not require dosage control



- Types
 - Continuous Spray
 - Metering Valve
- Continuous Spray
 - Product is released as long as pressure is maintained on the actuator.
- Metering valve
 - A finite Volume of product is released when the actuator is pressed.
 - No more product is released unless the actuator is returned to its rest position and repressed

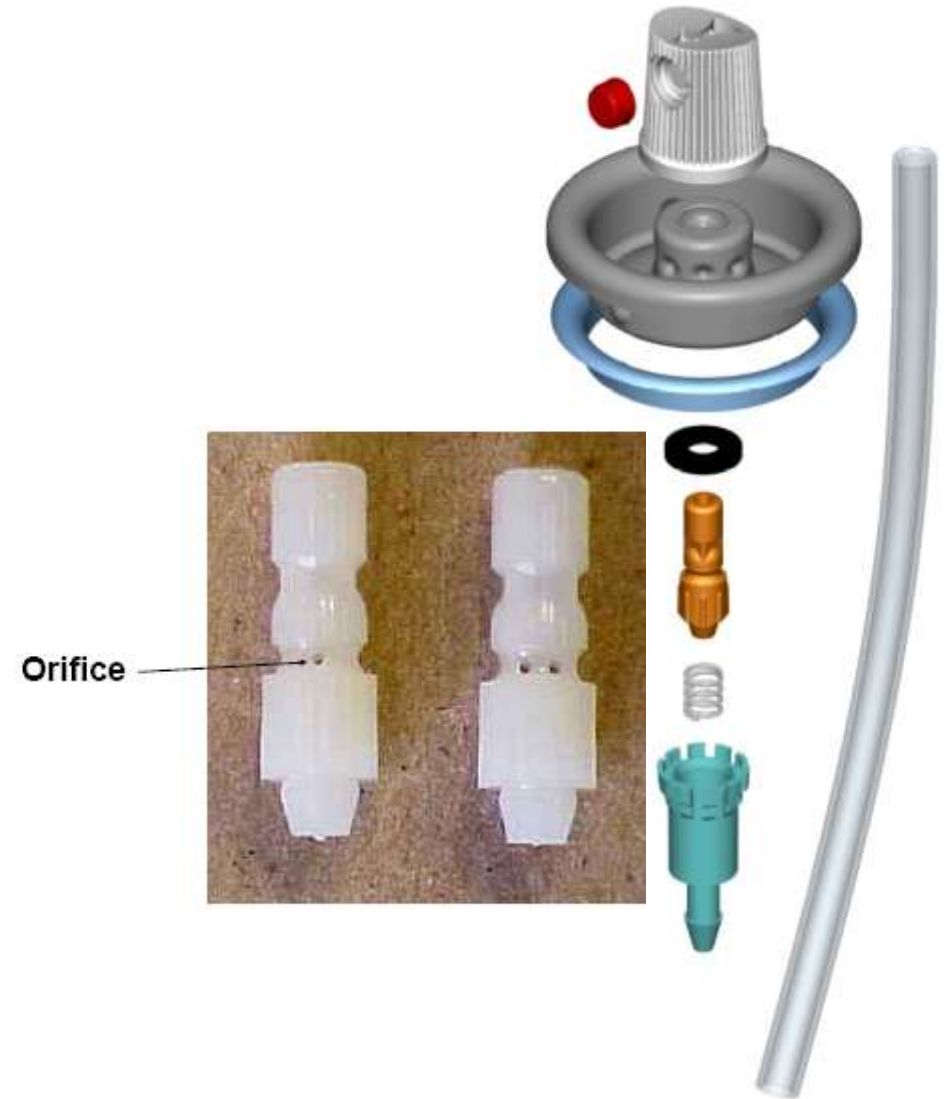
COMPONENTS of valve

- Actuator
 - Controls pattern and flow
- Ferrule or mounting cup (with mounting cup gasket)
 - The link between can and valve
- Stem gasket
 - The “on/off” switch
- Stem
 - Controls flow
- Spring
 - Closes the valve
- Housing or valve body
 - Encloses spring/stem
 - Controls flow
- Dip tube
 - Draws product up into the valve



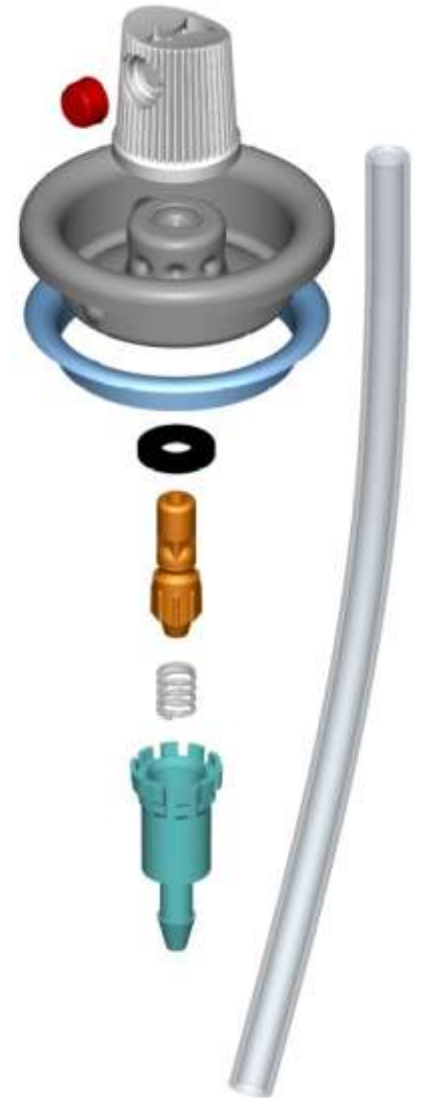
STEM

- Controls the flow
- The stem is made from
 - Nylon
 - Derin
 - Brass
 - Stainless steel.
- One or more orifice of about 0.013 inch to 0.030 inch to three orifices of 0.040 inch each.



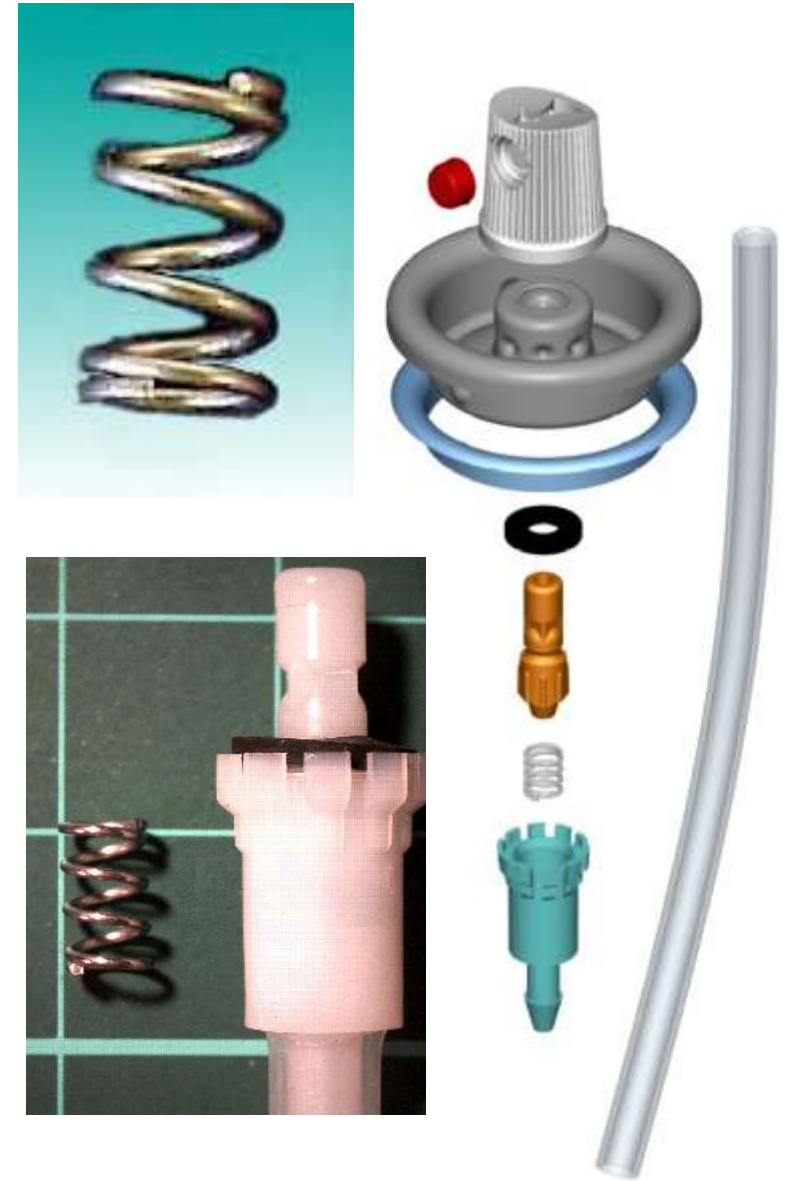
STEM GASKETS

- Covers the STEM orifice (The on-off switch)
- Different materials available for product compatibility.
 - BUNA N
 - NEOPRENE
 - BUTYL
 - VITON
- The stem gasket seals the valve.
- It is made of rubber and will shrink or swell with different formulations.
- There is no universal stem gasket!



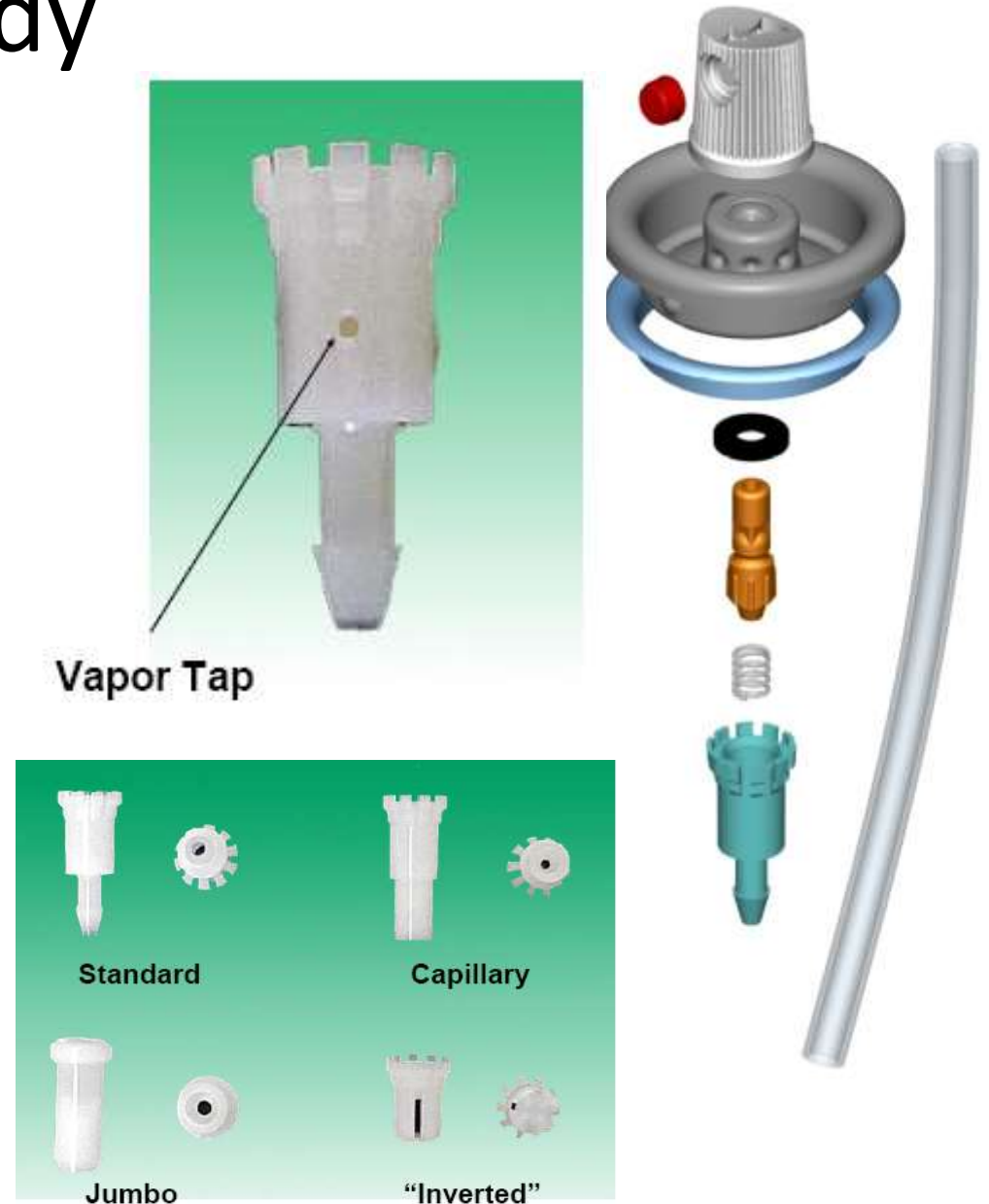
SPRING

- Spring serves to hold the gasket in place
- When the actuator is depressed and released, it returns the valve to its closed position.
- Stainless steel can be used with most aerosols



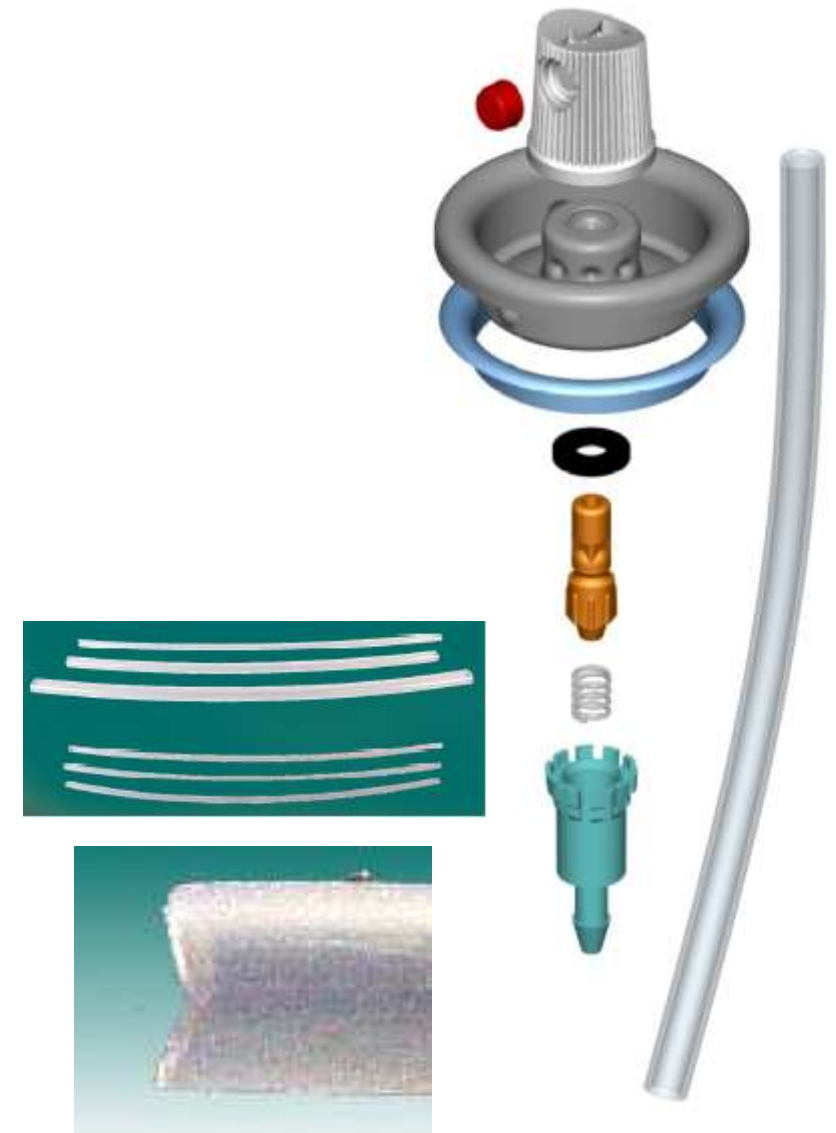
Valve Body

- Enclose the spring and stem
- Acts as a secondary metering orifice
- Wide range of orifice sizes 0.013" to 0.080"
- Manufactured from
 - Nylon or Delrin
- The housing may or may not contain another opening referred to as "vapor tap" (a hole in the side or bottom of the Housing) ranging in size from 0.005" to 0.080".
 - This allows the escape of vaporized propellant along with liquid product.
 - This produces fine particle size and prevents clogging with product containing insoluble materials.
 - Allows dispensing in inverted position.
 - Reduces chilling effect of the propellant on the skin
 - Do not use with compressed gas



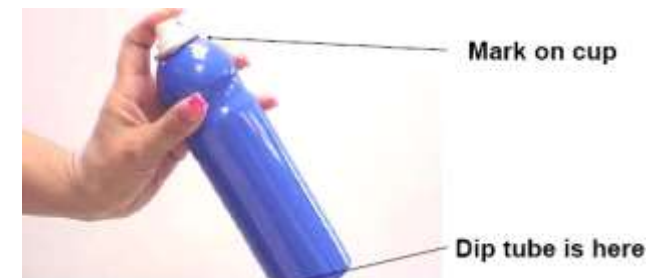
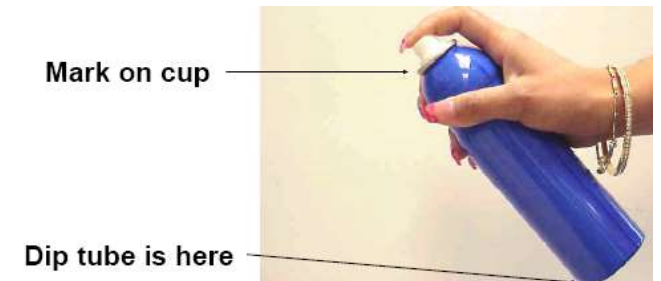
Dip tube

- Draws product up into the valve
- Made from
 - polyethylene or
 - polypropylene
- The inside diameter of commonly used dip tube are
 - Standard: 1/8" (0.122") inside diameter
 - Large: 3/16" (0.190") inside diameter
 - Jumbo: over 1/4" (0.260") inside diameter
 - Capillary: < 0.060" inside diameter
- Viscosity and the desired delivery rate plays an important role in the selection of the inner diameter of the dip tube.
- Notched to prevent closing off at bottom of can



Dip tube

- Use the dip tube curvature to your advantage
- Orient the dip tube for your particular application
 - Will ensure complete evacuation
 - orientation for downward spray (furniture polish, etc)
 - orientation for upward spray (Room fresheners, space sprays, etc.)

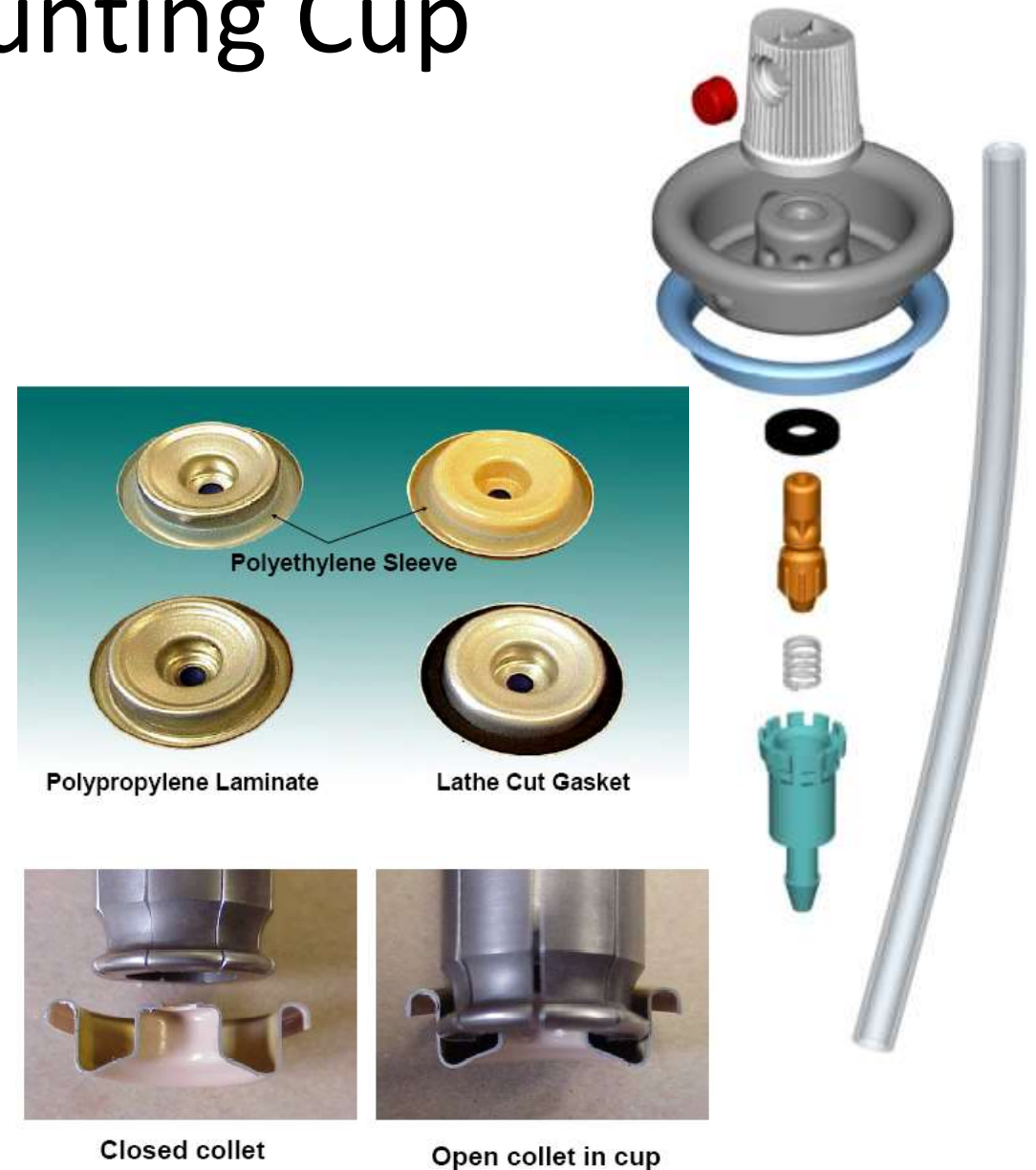


Ferrule or Mounting Cup

- Hold valve parts together
- Attaches valve to can
- It is attached to the container either
 - By rolling the end under the lip of the bottle or
 - By clinching the metal under the lip
- Made from
 - Tin plate steel
 - Aluminum
 - Brass
- They may be uncoated or be single or double epoxy/vinyl coated to increase resistance to corrosion.

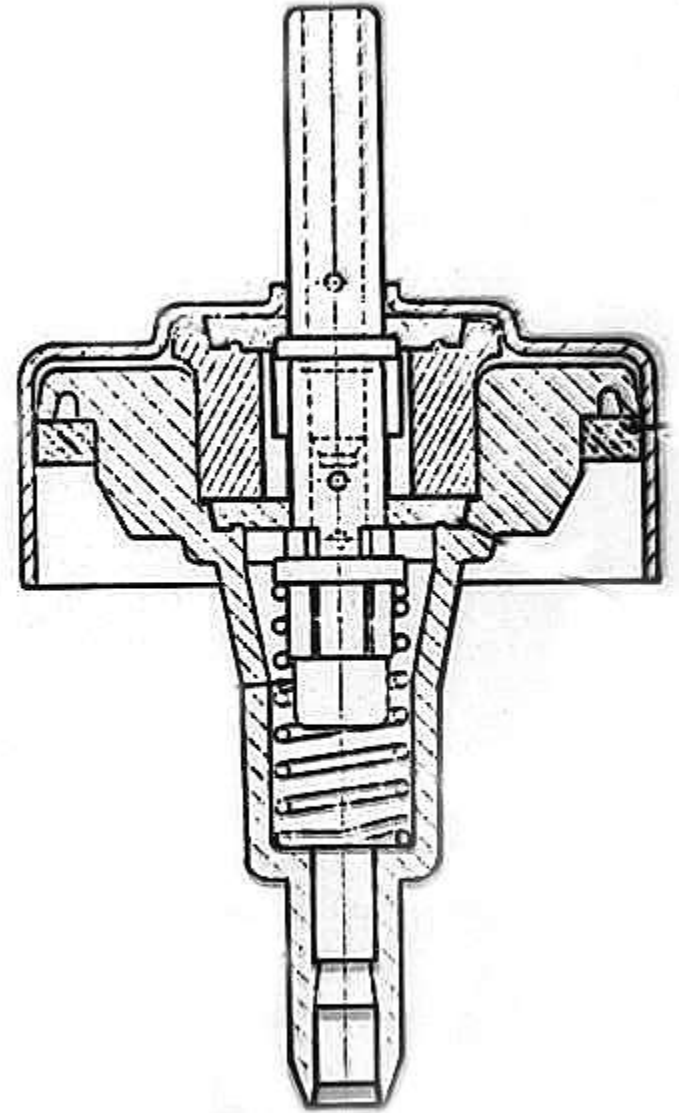
Gasket materials

- Provides a seal between cup and can
 - Polyethylene (PE) sleeve fully bonded to mounting cup
 - PP laminate (acts as coating and seal)
 - Cut gasket (aka lathe cut gasket) buna

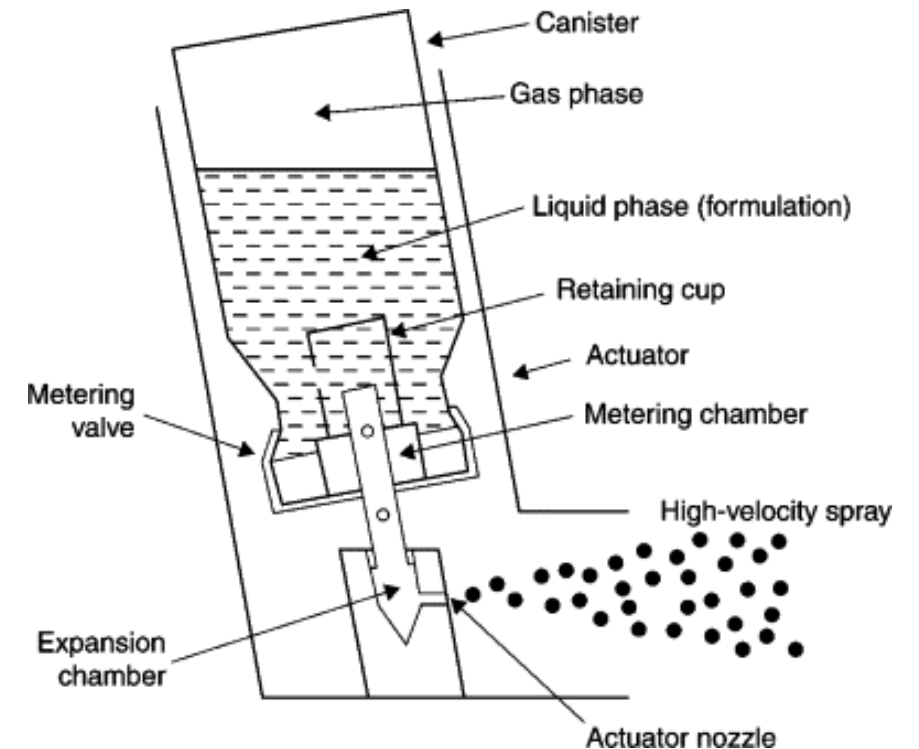
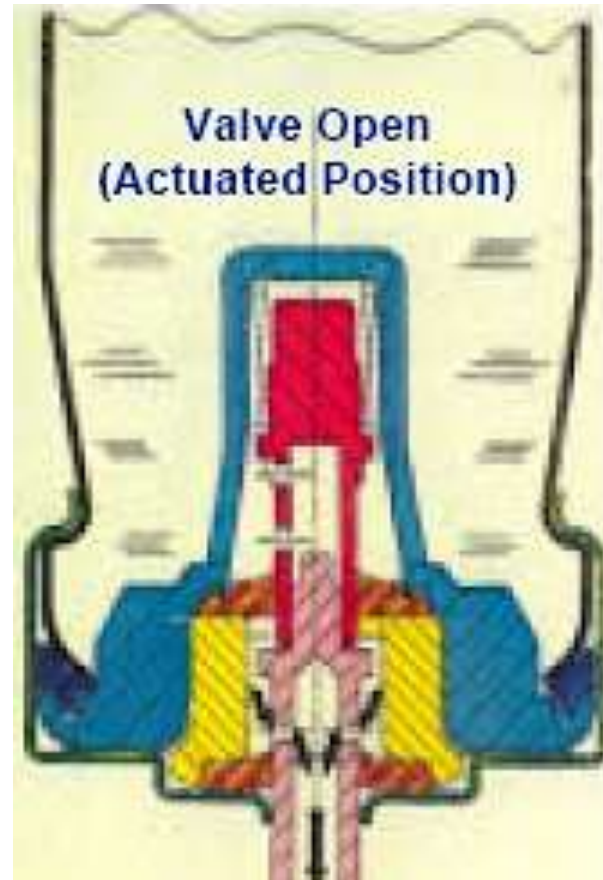
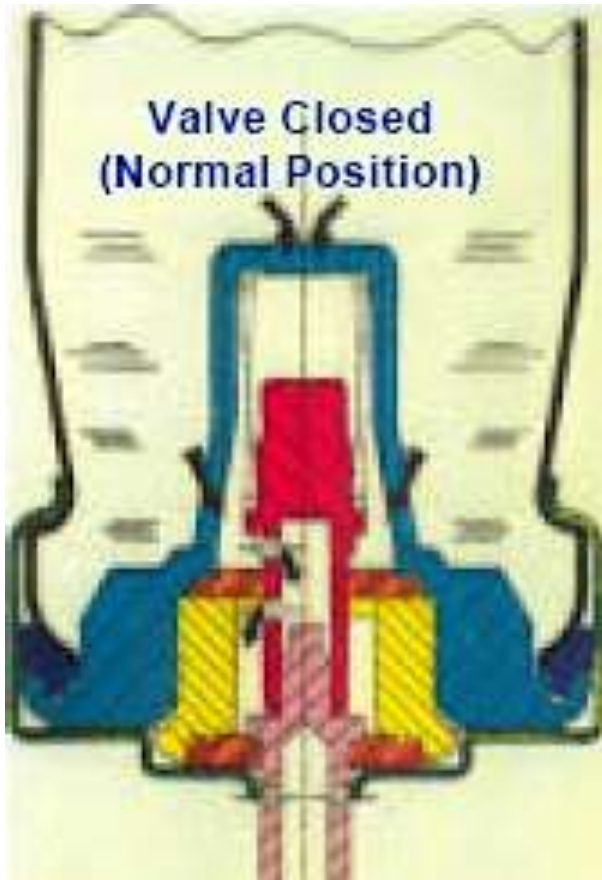


Metering Valves

- Metering valves are applicable to the dispensing of potent medication.
- These operates on the principle of a chamber whose size determines the amount of medication dispensed.
- Approximately (50 to 150mg) $\pm$ 10% of liquid material can be dispensed at one time with the use of such valve.



Metering Valve Operation



Actuators



Actuators

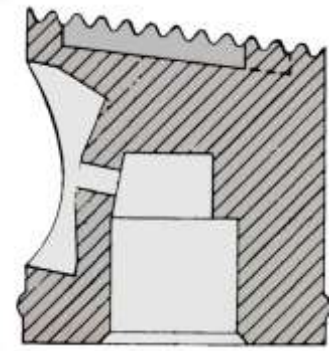
- Actuators allows easy opening and closing of the valve.
- It also serves to aid in producing the required type of product discharge.
- Gives way to site of application.
- There are many different types of actuators, Among them are those that produces
 - Spray
 - Foam
 - Solid stream
 - Special applications

Spray Actuators

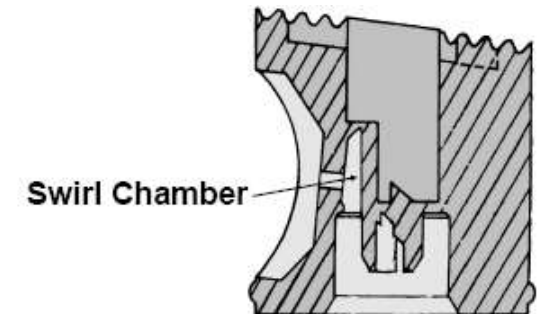
- When there is a large percentage of propellant mixture containing a sufficient quantity of a low boiling propellant such as propellant 12 or propane, actuators having relatively large orifices can be used.
- This combination of propellant vaporization and actuator orifice and internal channel can deliver the spray in the desired particle size range.
- A spray type actuator can be used with pharmaceuticals intended for topical use, such as spray on bandages, antiseptics, local anesthetics.

Spray Actuators

- When these actuators are used with aerosol products containing relatively low amount of propellant (50% or less), the product is dispensed as a stream rather than as a spray, since the propellant present in the product is not sufficient to disperse the product fully.
- For this products, a mechanical breakup actuators is usually used (opening of 0.016 inch to 0.040 inch in diameter).
- These actuators are capable of mechanically breaking a stream into fine particles by causing the stream to “swirl” through various channels built into the actuators.



- Non-mechanical breakup
- A direct flow through the actuator
- Usually results in a stream



- Mechanical break up
- Incorporates a swirl chamber
- gives discernable pattern size and shape



Foam Actuators

- These actuators consist of relatively large orifice ranging from approximately 0.07 inch to 0.125 inch and greater.
- The orifices allow for passage of the products into a relatively large chamber, where it can expand and be dispensed through the large orifice



Solid Stream Actuators

- The dispensing of semisolid products as ointment generally requires these actuators.
- Relatively large opening allow the passage of product through the valve stem and into the actuators.
- These are essentially similar to foam type actuators.



Special Actuators

- Many of the pharmaceutical and medicinal aerosols require a specially designed actuators to accomplish a specific purpose.
- They are designed to deliver the medication to the appropriate site of action e.g. throat, eye, nose etc.

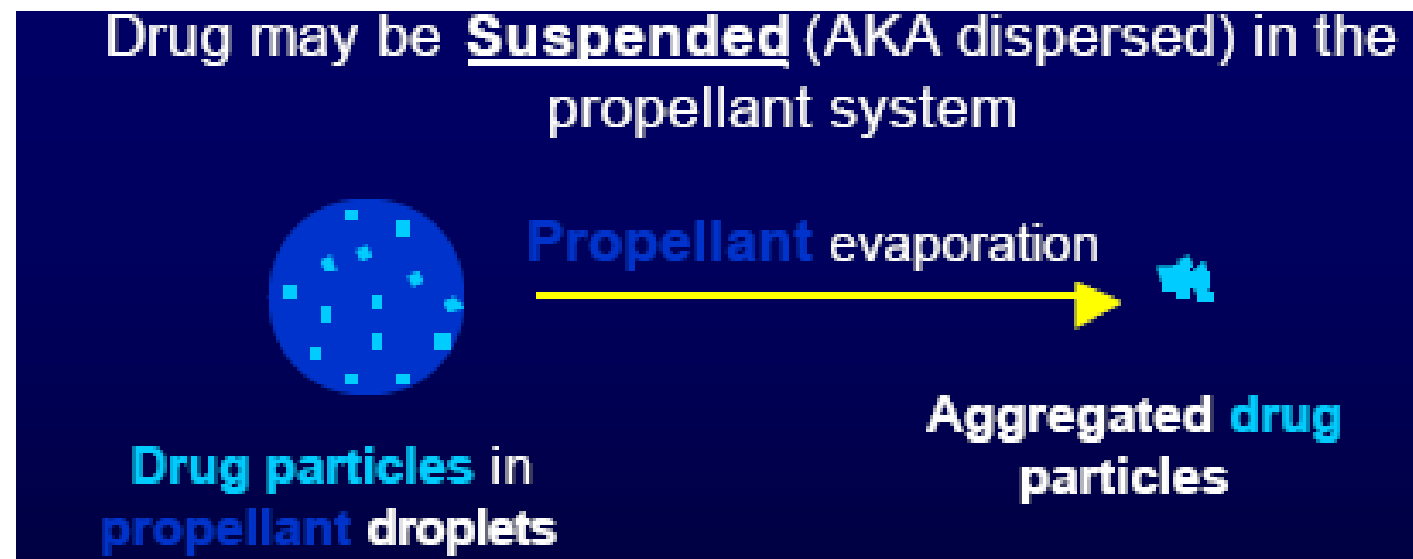
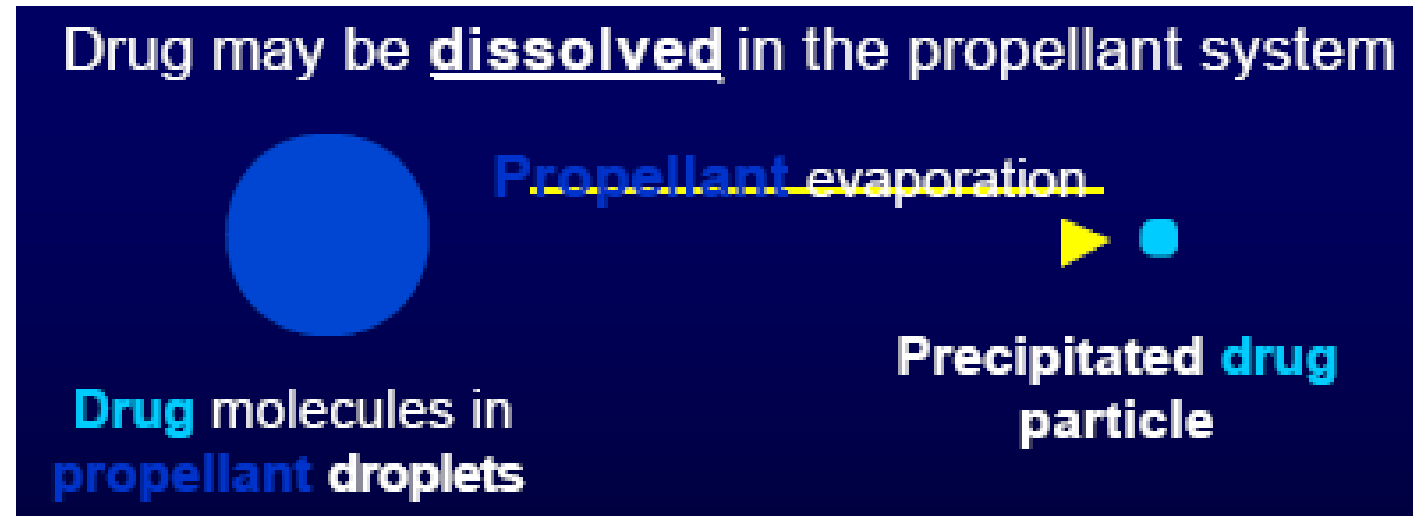


Formulation of pharmaceutical aerosol

- The aerosol formulation consist of two essential components:
- Product concentrate
 - Active ingredient(s)
 - Co-solvents (Ethanol, PG, Glycerol)
 - Antioxidants
 - Surfactants
- Propellant
 - Single propellant
 - Blend of propellants
(to give the desired vapor pressure, solubility, and particle size.)

Aerosol System

- This can be
 - 2phase system
 - Solution
 - (liquid-liquid, solid-liquid)
 - 3 phase system
 - Suspension
 - Solid-liquid
 - Emulsion
 - Liquid-liquid



The formulation of aerosols

Solution system

- When active ingredient(s) are soluble in the propellant, no other solvent is required.
- This formulation forms two-phase system of a vapor and liquid phase of propellant.
- Depending on the types of spray required, The propellant may consist of
 - Single propellant 12 or A-70 which produces fine particles (space spray).
 - Mixture of propellant 12 and other propellant with vapor pressure lower than that of propellant 12, this decreases the pressure of the system resulting production of large particle (surface coating spray).
 - Addition of less volatile solvents such as ethyl alcohol, propylene glycol, ethyl acetate, glycerin and acetone
- The amount of propellant used may vary from 5% (for foams) to 95% (for inhalation products) of the entire formulation.

The formulation of aerosols

Example1:

	<u>weight %</u>
Isoprenaline HCl	0.25
Ascorbic acid	0.10
Ethanol	35.75
Propellant 12	63.90

Here,

Ethanol is a cosolvent, less volatile solvent.

Ascorbic acid is antioxidant.

Example 2

	<u>weight %</u>
Octyl nitrite	0.1
Ethanol	20.0
Propellant 114	49.2
Propellant 12	30.7

Here,

Ethanol is a cosolvent, less volatile solvent.

Propellant 114 lowers the total vapor pressure

The formulation of aerosols

- Example of some combination of propellant and packaging considerations

Propellant 12/11 (30 : 70)

Propellant 12/114 (45 : 55)

Propellant 12/114 (55 : 45)

Pressure of above combination requires packaging in a metal container

Propellant 12/114 (20 : 80)

Propellant 12/114 (10 : 90)

Packing of combination can be done in glass container

The formulation of aerosols

Solution system of hydrocarbon propellants

<u>Example2:</u>	<u>weight (%)</u>
Active ingredients	up to 10-15
Solvents (ethanol etc.)	up to 10-15
Distilled water	10-15
Hydrocarbon propellant A-46	55-70

- Hydrocarbons are often used in topical aerosol.
- Depending on the amount of **water** present, the final product may be a solution or a **three-phase** system.
- Hydrocarbon propellant A-70 produces a drier particle, while propellant A-17 and A-31 tend to produce a wetter spray.
- These can be packed in plastic coated glass bottles, provided that it meets test requirements

The formulation of aerosols

Water-Based System (Emulsion)

- Relatively large amount of water is present which replace all or part of the non-aqueous solvents used in aerosols.
- Depending upon the formulation they are emitted as
 - * Spray or * foam
- In this system, active ingredient are solubilized with the help of solvents and dispersed in propellant.
- Surfactants with lower water solubility (low HLB value) are used to produce satisfactory homogeneous dispersion .
- When this type of product is dispensed, the propellant vaporizes and disperses the active ingredients into minute particles.
- The propellant content varies from 25% to 60%, but can be as low as 5% depending on the nature of the product
- To achieve the desired fine particle size with products containing large amounts of water and a low proportion of propellant , a mechanical breakup actuator must be used along with a vapor tap valve

The formulation of aerosols

Foam systems

Emulsion and foam aerosols consist of

- active ingredients,
 - aqueous or non-aqueous vehicle,
 - surfactant and
 - propellant
- These are dispensed as a stable or quick breaking foams depending upon the nature of ingredients and formulation.
 - The liquefied propellant is emulsified and is generally found in the internal phase.

The formulation of aerosols

Types

- Aqueous stable foams
 - Both hydrocarbons and compressed gas can be used, fluorocarbons are no longer allowed to use except on contraceptive foams
 - Total propellant content is usually as high as about 8 to 10%, 3% to 5% are common
 - Example steroids, antibiotics
- Non Aqueous stable foams
 - Various glycols such as polyethylene glycol are used.
 - Emulsifying agents of glycol ester class e.g. propylene glycol monostearate are used.
 - Various medicaments are incorporated in this base.
- Quick breaking foams
 - In this propellant are in external phase, when dispensed the product is emitted, which then collapse into a liquid
- Thermal foams
 - Produces a warm foam, e.g. shaving cream, hair color and dye
 - Products were discontinued owing to inconvenience of use, expense and lack of effectiveness, corrosion problem.

The formulation of aerosols

Suspension systems

In this there is dispersion of active ingredients in the propellant or mixture of propellant.

Example	weight %
epinephrine bitartrate (within 1 to 5 microns)	0.50
sorbitan trioleate(spans-85)	0.50
propellant 114	49.50
propellant 12	49.50

Here,

- Sorbitan trioleate: surfactants/suspending agents, to decrease the rate of settling of the dispersed particles.
- The epinephrine bitartrate has a minimum solubility in the propellant system, but is sufficiently soluble in the fluids in the lungs to exert a therapeutic activity.

The formulation of aerosols

- Problems in Suspension systems
 - The suspended particles may undergo Flocculation to Aggregation causing
 - Particle may adhere to the walls of container
 - Agglomeration may result in valve clogging
 - Inaccuracy of dosage
 - May damage the liner and possible metal container.
- Physical stability can be increased by
 - Control of moisture content of both suspensoid (drying) and the propellant (desiccation) below 300ppm

The formulation of aerosols

- Physical stability (contd....)
 - Use of derivatives of active ingredients having minimum solubility in propellant system but show solubility in the fluid so as to decrease particle size growth.
 - Reduction of initial particle size (grinding) in the range of 1 to 5 microns so as to decrease rate of agglomeration.
 - Adjustment of density of propellant and/or suspensoid (addition of higher or lower density compound) so that they are equalized which decreases rate of settling of the suspensoid.
 - Use of dispersing agents to reduce the rate of agglomeration and to act as a lubricant for the particles passing through valve orifices

Manufacture of pharmaceutical aerosols

Manufacture of aerosol takes place in two stages:

Step1: manufacture of concentrate (general procedure and condition)

- Concentrate is prepared according to generally accepted procedure and condition.
- The product concentrate is tested for its quality. (saves time and money)

Step2: Addition of propellant

- Cold filling
- Pressure filling

Since, part of the manufacturing operation takes place during filling operation, this necessitates special quality control measures during the filling operation to ensure that both concentrate and propellant are brought together in the proper proportion.

Manufacture of pharmaceutical aerosols

Cold filling:

- Restricted to non-aqueous products, and to those products not adversely affected by low temperatures (- 40°F).
- In this method, product concentrate is chilled to - 30°F to - 40°F and added to chilled container, followed by addition of chilled propellant.
- Alternatively, Both concentrate and propellant mixed and chilled to - 40°F pressure vessel and added to chilled container.
- After addition, valve is crimped in place, and subjected to quality test.

Cold filling line

Unscrambler, air cleaner, concentrate filler (with chilling facility), propellant filler (with chilling facility), valve placer, valve crimper, water bath, labeler, coder and packing table

Manufacture of pharmaceutical aerosols

Pressure filling:

- preferable for solution, emulsions, suspensions, which can not be chilled.
- less danger of contamination of the product with moisture; high production speeds; less propellant loss.
- In this the concentrate is added to the container at room temperature, and valve is crimped in place.
- The propellant is added around and through the valve stem or “under the cap”.
- For those products adversely affected by the air in headspace is evacuated prior to adding the propellant.

Production line

Unscrambler, air cleaner, concentrate filler, valve placer, purger and valve crimper, pressure filler, water bath, labeler, coder and packing table.

Quality Control for Pharmaceutical Aerosols

- Propellants
 - Propellant shipped are sampled
 - Tested as per specification
 - If as per specification are piped to storage tank.

Sample undergoes following tests

- Identification (GC)
 - Composition when blend of propellant is used
 - Vapor pressure measurement
 - Density measurement
 - Purity and acceptability is tested by determining moisture, halogen and non-volatile residue.
- “ All suppliers of propellant conducts mentioned tests in their own laboratories, and the test that are run by the user are generally a check on these results, and ensure that the propellants have not been contaminated during shipment.”

Quality Control for Pharmaceutical Aerosols

- Containers

Test

- Examined for defects in lining
- Weight of bottles
- Flaw examination for glass
- Dimension of the neck and other part
- Degree of conductivity of an electric current as a measure of the exposed metal.

Weight checking

- This is usually accomplished by periodically adding to the filling line the tarred empty aerosol container, which after being filled with concentrate/ propellant, are removed and then accurately weighed.

This process is used to check the

- Weight of concentrate
- Weight of Propellant (of proper combination also)
- Finished product (Accuracy of the filling operation)

Quality Control for Pharmaceutical Aerosols

- Valves, Actuators, and Dip tubes

The magnitude of the valve delivery and the degree of uniformity between the individual valves is assessed

Valve acceptance

For valves delivering 54 μ l or less, limit is $\pm 15\%$

For valve delivering 55 μ l to 200 μ l, the limit is $\pm 10\%$

- i. Of the 50 individual deliveries, if 4 or more are outside the limit-Reject
- ii. If 3 are outside the limit, another 25 are sampled and tested, if >1 is outside, sample is rejected
- iii. If 2 deliveries from one valve are outside the limit, 25 more sampled and accepted if NMT 1 is outside the specification.

Quality Control for Pharmaceutical Aerosols

- Leak testing
 - 130°F under water in leak test tank
- Spray testing
 - Serves to clear the dip-tube and to check for defects in valves and spray pattern

Testing of pharmaceutical aerosols

A. Flammability and combustibility

1. Flash point of limited value

- Standard TAG OPEN CUP Apparatus is used.
- The chilled aerosol (-25°F) is transferred to the test apparatus
- The temperature of test liquid is allowed to increase slowly and the temperature at which the vapor ignites is taken as a flash point

2. Flame extension

- This test indicates the effect of an aerosol formulation on the extension of an open flame.
- The product is sprayed for about 4 sec into a flame. Depending on the nature of the formulation, the flame is extended, the exact length is measured with a ruler

Testing of pharmaceutical aerosols

B. Physicochemical characteristics

1. Vapor pressure:

- Vapor pressure is measured by using pressure gauge.
- water bath, and special equipments can also be used.
- pressure variation from container to container is determined, excessive variation indicates the presence of air in the headspace

2. Density: hydrometer or pycnometer

3. Moisture content: Karl Fisher method, GC

4. Identification of propellants: GC, IR

5. Concentrate-propellant ratio: GC

Testing of pharmaceutical aerosols (continued)

C. Performance

1. Aerosol valve discharge rate

- Initial weight of Aerosol is taken, the container is discharged for a given period of time using standard apparatus.
- The container is reweighed after time limit.
- The change in weight per time dispensed is the discharge rate and expressed as grams per seconds; $(W_1 - W_0)$ g/s

2. Spray pattern

- Method is based on the impingement of the spray on a piece of paper that has been treated with a dye talc mixture
- Depending upon the nature of aerosol, an oil soluble dye or water soluble dye is used.
- Particles that strikes the paper cause the dye to go into solution and to be absorbed into the paper.
- The pattern give the record of the spray and can be used for comparison purpose

Testing of pharmaceutical aerosols

3. Dosage with metered valves:

- Reproducibility of dosage each time the valve is depressed:

This can be determined by assay technique

a) one or two doses are dispensed into a solvent or onto a material that absorbs the active ingredient. This is then assayed.

b) Accurate weighing of the filled container followed by dispensing of several doses, the container is reweighed and difference in weight divided by the number of dispenses gives the average dose. This must be repeated and the results compared.

- Amount of medication actually received by the patient:
 - a) hard to determine; b) artificial respiratory system

Testing of pharmaceutical aerosols (continued)

4. Net contents: $W_{\text{total}} - W_{\text{container}}$

5. Foam stability:

- visual evaluation, rotational viscometer, rod falling, mass penetration

6. Particle size determination:

- cascade impactor: 0.1~30 microns
- light scatter decay: Tyndall beam

7. Leakage

D. Biologic characteristics

1. Therapeutic effect

2. Toxicity